UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION

+ + + + +

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
MEDICAL DEVICES ADVISORY COMMITTEE

+ + + + +

CIRCULATORY SYSTEM DEVICES PANEL

+ + + + +

MEETING

+ + + + +

TUESDAY,
SEPTEMBER 21, 2004

+ + + + +

The Panel met at 9:00 a.m. in Salons A, B, and C of the Hilton Gaithersburg Washington, D.C./North, 620 Perry Parkway, Gaithersburg, Maryland, Dr. William H. Maisel, Acting Chairperson, presiding.

PRESENT:

WILLIAM H. MAISEL, M.D., M.P.H., Acting Chairperson
LANCE BECKER, M.D., Consultant
JEFFREY A. BRINKER, M.D., Consultant
THOMAS G. BROTT, M.D., Consultant
ALFRED HALLSTROM, Ph.D., Consultant
HENRY HALPERIN, M.D., Consultant
NORMAN S. KATO, M.D., Consultant
JOHN MARLER, M.D., Consultant
MICHAEL C. MORTON, Industry Representative
LINDA MOTTLE, Consumer Representative
SHARON-LISE NORMAND, Ph.D., Voting Member
JOSEPH P. ORNATO, M.D., Consultant
JOHN C. SOMBERG, M.D., Consultant

PRESENT: (cont'd)

JUDAH Z. WEINBERGER, M.D., Ph.D., Consultant
MYRON WEISFELDT, M.D., Consultant
CLYDE YANCY, M.D., Consultant
GERETTA WOOD, Executive Secretary

FDA REPRESENTATIVES:

BRAM ZUCKERMAN, M.D., Cardiovascular Devices
RANDALL BROCKMAN, M.D.
RICHARD FELTEN, M.S.
ELISA HARVEY, D.V.M.
RONALD M. LAZAR, Ph.D., Consultant
NEIL OGDEN, M.S.
JULIE A. SWAIN, M.D., Consultant
ELIZABETH J. TRITSCHLER, M.S.E.
CELIA WITTEN, Ph.D., M.D., General Restorative and Neurological

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

(9:04 a.m.)

ACTING CHAIRPERSON MAISEL: Good morning. Why don't we get started?

I'd like to call to order this meeting of the Circulatory System Devices Panel. Today's topic is discussion of the type of data required to effectively evaluate the performance of CPR and hypothermia devices.

And I'll ask Geretta Wood to read the conflict of interest statement, please.

MS. WOOD: The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. However, the agency has

determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government.

Therefore, waivers have been granted for Drs. Lance Becker, Alfred Hallstrom, Normand Kato, Joseph Ornato, Judah Weinberger, and Clyde Yancy, for their interest in firms that could potentially be affected by the Panel's recommendations. The waivers allow these individuals to participate fully in today's deliberations.

A limited waiver has been granted to Dr. Henry Halperin for his interest in a firm. The limited waiver allows him to participate in the review and discussion, but excludes him from voting. A copy of the waivers may be obtained from the agency's Freedom of Information Office, Room 12A-15, of the Parklawn Building.

We would like to note for the record that the agency took into consideration other matters regarding Drs. Becker, Brinker, Halperin, Ornato, and Yancy. These panelists reported past or current

interest involving firms at issue, but in matters that are unrelated to today's agenda.

Drs. Weisfeldt and Halperin also reported past and or current interest in firms at issue. The agency has determined that these individuals may participate in the Panel discussions.

The agency also would like to note that Dr. William Maisel has consented to serve as the Chair for the duration of this meeting.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement, and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firms whose products they may wish to comment upon.

ACTING CHAIRPERSON MAISEL: I'd now like to have the Panel members introduce themselves. I'm

William Maisel, a Cardiologist at Brigham & Women's Hospital.

And why don't we start with Dr. Zuckerman on my left, please.

DR. ZUCKERMAN: Bram Zuckerman, Director, FDA Division of Cardiovascular Devices.

DR. BECKER: I'm Lance Becker, an Emergency Medicine Physician, at the University of Chicago.

DR. HALPERIN: Henry Halperin. I'm a Clinical Electrophysiologist at Johns Hopkins.

DR. WEISFELDT: I'm Myron Weisfeldt. I'm Chair of the Department of Medicine at Johns Hopkins.

DR. BROTT: Tom Brott. I'm a Neurologist at Mayo Clinic.

MR. MARLER: John Marler. I'm a Neurologist at the National Institute of Neurological Disorders and Stroke, NIH, and head the Clinical Trial Group there.

DR. HALLSTROM: Al Hallstrom. I'm a Professor of Biostatistics at the University of Washington.

DR. KATO: Norman Kato, Cardiac and Thoracic Surgery, Encino, California.

MS. WOOD: Geretta Wood, Executive Secretary.

DR. ORNATO: Dr. Joe Ornato, Chairman of Emergency Medicine and also a Cardiologist at Virginia Commonwealth University Medical Center, Richmond, Virginia.

DR. NORMAND: Thanks. I'm Sharon-Lise Normand, Professor of Health Care Policy and Biostatistics at Harvard Medical School and Harvard School of Public Health.

DR. SOMBERG: I'm John Somberg, Professor of Medicine and Pharmacology at Rush University in Chicago.

DR. BRINKER: Jeff Brinker, Johns Hopkins.

DR. YANCY: Clyde Yancy, UT Southwestern, and Cardiologist and Professor of Medicine.

DR. WEINBERGER: Judah Weinberger, Director of Interventional Cardiology, Columbia, New York.

MS. MOTTLE: Linda Mottle, Director of

Clinical Research Program, Gateway College in Phoenix, Consumer Rep.

MR. MORTON: Michael Morton. I'm the Industry Rep. I'm employed by Sorin Group.

ACTING CHAIRPERSON MAISEL: Thank you.

At this point, I'd like to invite the FDA to give their presentation.

DR. BROCKMAN: Good morning. I'd like to outline the order of the FDA's presentations this morning. I'm Randall Brockman. I'll give a brief clinical history of CPR devices. Elizabeth Tritschler will provide a regulatory history of CPR devices. Dr. Ronald Lazar will discuss neural events and outcomes in cardiac arrest clinical trials. And Dr. Elisa Harvey will discuss exception from informed consent in CPR device trials. Geretta Wood will then present the FDA's questions to the panel.

Well, I'm Randy Brockman. I'm a Cardiac Electrophysiologist with the FDA. I'd like to address some important issues in clinical trial design for new CPR devices, and I'd like to provide a clinical summary of the history of CPR and its devices to

assist with the first goal. There will be a separate session on post-arrest hypothermia this afternoon.

Well, there's ample evidence of the important impact of chain of survival function on survival of out-of-hospital cardiac arrest. Early defibrillation, in particular, has emerged as an important intervention. We've seen numerous interventions at various points along this chain.

And while some have resulted in improvements in short-term success, such as return of spontaneous circulation and short-term survival, a few interventions have resulted in improvements in hospital discharge and improvements in neurologic outcome.

It'll be important for future trials to evaluate appropriate success endpoints. How should we define those endpoints? Should a study of a new investigational device have to demonstrate improvement in hospital discharge rates and neurologic outcome when this encompasses the entire chain of survival? Alternatively, could such trials be designed to evaluate a short-term endpoint with additional trials

adding to the database?

Following is a brief history of some of the published treatment interventions in cardiac arrest. My goal is to highlight the results of these reports and to use these results as a framework to decide on appropriate endpoints for future CPR trials.

Just from a historical perspective, resuscitation of patients who have experienced a cardiopulmonary arrest has been attempted for over a century. In the 1950s, Safar and Elam sort of rediscovered, if you will, a mouth-to-mouth ventilation by reading how midwives use the technique to revive newborns. But until 1960 no successful resuscitation was limited to victims of respiratory arrest.

In 1960, Kouwenhoven described that forceful chest compressions, closed chest cardiac massage, produced respectable arterial pulses. Combined, these two techniques form the critical steps of modern CPR, and they've been practiced for more than 40 years.

The success rates following in-hospital

cardiac arrest have remained essentially unchanged over the last three to four decades, with return of spontaneous circulation in about 30 percent of patients and approximately 15 percent of patients being discharged neurologically intact.

In a randomized control trial of in-hospital cardiac arrest, interposed abdominal counterpulsation demonstrated improvement in the rate of return of spontaneous circulation with about 51 percent in the IAC group versus about 27 percent in the standard CPR group.

At-hospital discharge, a significantly greater proportion of patients was alive in the IAC group versus the hospital discharge -- excuse me, versus the standard CPR group. That was 25 percent versus about 7 percent.

The rate of patients discharged neurologically intact was not statistically significantly different in the IAC CPR group compared to the standard CPR group. While there was a trend, it was 17 percent versus 6 percent. That was not statistically significantly different.

Patients who suffer an out-of-hospital cardiac arrest have even worse outcomes than those who are resuscitated in the hospital, with hospital admission rates between 8 and 22 percent, and between 1 and 8 percent being discharged neurologically intact.

This has been largely unchanged despite additions to the basic components of CPR, such as high-dose epinephrine, transcutaneous pacing, and vest CPR. Techniques such as active compression-decompression CPR, with or without inspiratory impedance threshold devices, have demonstrated mixed findings. And AEDs have demonstrated improved survival.

I'm going to briefly go through some of this data. In one study of high-dose epinephrine -- this was an unblinded, randomized control trial of over 3,300 patients -- high-dose epinephrine compared to standard-dose epinephrine resulted in a higher rate of return of spontaneous circulation, about 40 percent versus about 36 percent, and survival to hospital admission about 26 percent versus about 23 percent.

But there was no difference in the rate of survival to hospital discharge or neurologic status.

In two other trials, both double-blinded, randomized control trials, totalling over 1,900 patients, high-dose epinephrine failed to demonstrate any substantial improvement in neurologic outcome or survival.

Vest CPR includes a pneumatically-cycled, circumferential, thoracic vest system, which is used to augment intrathoracic pressure during CPR. In a small, unblinded, randomized control trial -- this was in-hospital cardiac arrest -- there was a trend towards increase in return of spontaneous circulation and 24-hour survival, but there was no difference in survival to hospital discharge.

And then, in an unblinded, concurrent controlled trial, which evaluated the effect of transcutaneous pacing and out-of-hospital asystolic cardiac arrest, no improvement was found in the rate of survival to hospital admission or the rate of survival to hospital discharge.

Active compression-decompression CPR uses

a suction-like device applied to the sternum to allow active chestwall decompression in order to enhance negative intrathoracic pressure during the decompression phase. The goal is to enhance venous blood return.

Active compression-decompression CPR compared to standard CPR has demonstrated mixed findings. Two studies -- by the way, the numbers here correlate to my references in the Panel pack. Two studies, both unblinded, group crossover control trials of out-of-hospital cardiac arrest, totalling over 1,400 patients, demonstrated no difference in survival to hospital admission, survival to hospital discharge, or neurologic outcomes.

However, a different study -- this was an outside U.S., unblinded, parallel group crossover design, with 750 victims of out-of-hospital cardiac arrest. The study compared ACD-CPR to standard CPR, and demonstrated an improvement in return of spontaneous circulation. It was about 45 percent versus 30 percent in the standard CPR group.

Improvement in 24-hour survival was 26

percent versus about 13 percent, and hospital discharge without neurologic impairment -- and this was about 5-1/2 percent versus 2 percent. This latter study, which demonstrated improved outcomes, differed from the other two in that a physician was present on the scene of the arrest to guide ACLS therapy. And, in addition, the EMS personnel involved had been using the ACD-CPR techniques for several years, raising the possibility of a learning curve effect.

Inspiratory impedance threshold devices have been combined with ACD-CPR devices. Inspiratory impedance threshold devices are designed to help maintain the increased negative intrathoracic pressure generated during active decompression in order to augment venous return.

Comparing ACD-CPR plus the ITD, the inspiratory impedance threshold device, to standard CPR, two studies -- both were randomized control trials involving over 600 patients -- demonstrated these devices to increase the 24-hour survival rates. In the first trial it was 37 percent versus about 22 percent. In the second trial it was 32 percent versus

22 percent. But were not found to change the survival to hospital discharge rates.

In the first trial it was 18 versus 13 percent. In the second one it was 5 versus 4. The first trial excluded subjects for whom the known time from collapse to initiation of CPR was greater than 15 minutes. The second one excluded patients for whom the known time from collapse to initiation of CPR was greater than 30 minutes. I think that difference likely explains the difference in survival to hospital discharge rates.

I present most of this just to demonstrate the notion that short-term survival does not necessarily predict long-term survival.

On the other hand, AED seemed to improve more than short-term survival and out-of-hospital cardiac arrest. The two trials I present here are both single-arm, unblinded trials of out-of-hospital arrest. The first one is the CASINO study, and when compared to published survival rates patients who received early defibrillation from an AED had an improved survival-to-hospital discharge of about

53 percent for VF arrest patients and 38 percent for all-cause arrest patients.

And then, in the second trial -- this is the long-term outcomes of out-of-hospital cardiac arrest after successful early defibrillation with an AED study -- when compared to published rates of about 1 to 8 percent, there was an improvement in the rate of hospital discharge with intact neurologic function of 40 percent. I'd note this trial evaluated VF arrest only, and the published rates are for all cardiac arrest.

A recently-published study of public access defibrillation, the PAD trial, demonstrated improvement in survival to hospital discharge -- 23 percent versus 14 percent for the standard CPR. The survivors had similar functional status.

So, in summary, survival rates with intact neurologic function have changed little over the past 30 to 40 years. Recent medical devices, such as AEDs and possibly ACD-CPR, plus or minus the impedance threshold devices, appear to be capable of having an impact. Choosing appropriate endpoints for clinical

trials will be important to determine which devices will facilitate improvement in long-term outcome.

Will additional improvements in the chain of survival also lead to additional quality of life benefit in those who survive cardiac arrest? And, more importantly, can we accept short-term improvement survival as a marker for long-term improvement?

Conversely, in light of the chain of survival concept, is it reasonable to expect an individual medical device to lead to long-term improvement, or can we accept improvements in each step along the chain with the ultimate goal of improving long-term outcomes when each step along the chain is strengthened?

And, finally, fostering an environment to enhance clinical research in this field will be important.

Thank you. And now I'd like to introduce Elizabeth Tritschler, who will give you a regulatory history of CPR devices.

MS. TRITSCHLER: Hi. My name is Elizabeth Tritschler, and I'm an Engineering Reviewer in the

Division of Cardiovascular Devices. Today I will brief you on the regulatory history of CPR devices.

The regulation of CPR devices can be broken down into three categories. The first category, which has been regulated since the 1970s, contains devices that mechanically assist the rescuer in chest compressions. Then, we have a new generation of devices in the 1980s, and these devices provide the rescuer with feedback regarding the compression depth and frequency.

And the 1990s brought a third generation of CPR devices, which are significantly different than the first two generations in that they are intended to enhance CPR hemodynamics. Now that we've seen this overview of the three types of devices that we have reviewed, I'm going to go into details about how the FDA has reviewed these types of devices.

And, first, I will start with external cardiac compression devices. The Medical Devices Amendment was passed in 1976, and a few months later we saw the first marketing clearance for an external cardiac compression device. Many more submissions for

external cardiac compression devices have been reviewed and cleared for marketing since 1976. These devices all contain some form of chestpiece. Some also contain a backboard.

The manual external cardiac compression devices require the rescuer to determine the rate of compression as in standard CPR. And then we have some external cardiac compression devices that are automated and provide compressions at a fixed rate.

These devices are intended to assist the rescuer by reducing the work required to compress the victim's chest and/or by distributing the compression force more evenly over the sternum. By reducing the work required to compress the victim's chest, these devices reduce the potential for rescuer fatigue.

External cardiac compression devices are Class III products and are reviewed through the 510(k) pre-market notification process in which the sponsor demonstrates substantial equivalence to a pre-amendment or previously cleared predicate device.

Generally, external cardiac compression device submissions do not contain clinical data due to

the similarities in design and technological characteristics to predicate devices.

And now we have the second generation of CPR devices. These were introduced a decade later in the 1980s with the first marketing clearance for a cardiopulmonary resuscitation aid device in 1984. CPR aid devices provide audible indicators of compression rate and/or visual indicators of compression depth.

It should be noted that in reviewing these devices the agency has worked with the sponsors to ensure that the device specifications are consistent with the AHA guidelines. These guidelines put out by the American Heart Association suggest appropriate rates and depths of compression for different patient populations.

These devices are designed with force gauges and a corresponding display. However, achieving a specific depth of compression can require different amounts of force in different patients due to variations in patient size and chest wall compliance.

Therefore, the device labeling for CPR aid

devices instructs the rescuer to perform the first chest compression per standard CPR -- in other words, to just eyeball the appropriate chest compression depth. And then, to note the force displayed on the device when the depth is achieved.

Then, for subsequent compressions on that patient, the rescuer can just watch the force gauge to make sure he or she is providing compressions with the appropriate amount of force to compress the patient's chest to the depth specified in the AHA guidelines.

These devices are intended to assist rescuers simply by providing feedback to help them maintain compliance with AHA guidelines for CPR. This feedback is especially helpful to fatigued rescuers who might otherwise be providing weakened compressions without even realizing they're doing so.

Like external cardiac compression devices, CPR aid devices are Class III products and are also regulated through the 510(k) pre-market notification process. Generally, 510(k) submissions for CPR aid devices do not contain clinical data due to the similarities in design and technological

characteristics to predicate devices.

And in the early 1990s, we saw the emergence of a third generation of CPR devices -- those devices intended to enhance CPR hemodynamics. Some examples of these types of devices -- and some of these Randy has already spoken about -- include interposed abdominal compression devices, active compression and decompression devices, circumferential chest compression devices, and minimally invasive open chest cardiac massage.

The agency made some precedent-setting regulatory decisions in the early 1990s regarding these devices. First, the agency determined that no pre-amendment or previously-cleared predicate device exists for CPR devices intended to enhance hemodynamics. Second, the agency determined that submissions for devices capable of enhancing CPR hemodynamics would require clinical data to support such claims.

So clinical studies for CPR devices have evaluated various primary and secondary endpoints, such as survival to admission to the ICU, survival to

24 hours, end tidal carbon dioxide, presence of a pulse during CPR, and various neurological evaluations at different time points ranging from 30 days to one year.

And some of these evaluations are based on CPC -- cerebral performance categories -- the Glasgow Coma Score, and other quality of life assessments. And Dr. Lazar will be going into more details regarding the neurological endpoint shortly.

On June 29th -- I know there's a typo in the slide. It should be June 29, 1998 -- this Panel met regarding a PMA for an active compression and decompression device. The device was intended to increase negative intrathoracic pressure thereby causing increased ventricular filling, increased cardiac output, and increased coronary artery and cerebral circulation.

The Panel recommended the submission be found not approvable due to problems with the clinical data such as lack of randomization at all sites and substantial OUS data used to support success. OUS data is problematic in that the treatment methods and

outcomes are affected by variations in the EMS systems in other countries compared to the United States.

And six years later we're here with a meeting of the Circulatory System Panel to discuss CPR devices. And where are we now? Well, we have over 30 cardiac compression devices cleared for marketing. We have a handful of cardiopulmonary resuscitation aid devices cleared for marketing, and there are no devices intended to enhance CPR hemodynamics approved for marketing in the United States.

So today we're asking the help of the Panel in identifying appropriate clinical trial endpoints and a scientifically sound and feasible clinical trial design in order to advance the science and medical therapies for this patient population.

And now Dr. Ron Lazar, who is a neuropsychologist at Columbia University in the Stroke and Critical Care Division, will discuss neurological and functional endpoints.

DR. LAZAR: Thank you. Of the many end organ effects of cardiac arrest, I think few would doubt that the impact on the brain is something of

extreme significance. And what I'd like to do this morning is spend a little bit of the time I have talking a little bit about the pathophysiology, the functional impact of cardiac arrest neurologically, and some issues regarding the measurement of cerebella outcomes.

I think to start off the process I think we need to discuss a little bit about the cascade of events as they occur in the brain. This is the -- a very brief description of what happens during the course of cerebral ischemia. If we start at the left, at the time of the cardiac event, shortly thereafter, in an effort to maintain cerebral blood flow, arterials expand in order to maintain cerebral profusion. And they will continue expanding until at the point they're maximally dilated and are no longer able to expand further.

At this point, cerebral blood flow diminishes, and in order to maintain oxygen metabolism, noted by the line here, the neurones demand increased oxygen, and you have an increase in the oxygen extraction fraction.

At the point that all the oxygen has been extracted from the blood, profusion has dropped, we go from a point of aerobic metabolism of the neurones to anaerobic metabolism. And during this period of time denoted as ischemia, the cell begins to degenerate in a very systematic fashion. And over the course of time enough of the elements degenerate until eventually infarction occurs.

It is this period of time during cerebral ischemia where the critical period for CPR exists. So that the longer we traverse this interval the more extensive and more permanent the injury is going to be.

This is a CAT scan of a case reported in The New England Journal last year of a 50-year-old female with a sudden loss of consciousness with no measurable pulse or blood pressure, and breathing and circulation returned spontaneously reportedly within a few minutes.

And one hour after the ER presentation this scan of the brain on the left shows the early signs of the cerebral injury. But you will note that

the sulci are still apparent, and you have fairly normal ventricular size. But after about four hours from this cardiac arrest the ventricles are now compressed, the sulci have been effaced, secondary to the cytotoxic edema arising from infarction. And this patient obviously did very poorly.

Going from the anatomy described in a CAT scan to the physiology in a PET scan, here we see the case of a patient who regained consciousness on -- and this is day two -- where at the top we have cerebral blood flow, on the bottom we have oxygen metabolism.

And you can see here that although there is blood flow going to the brain adequate to ordinary support function, because of the cardiac arrest, the blue areas denoted here indicate poor oxygen metabolism. And as a result, the brain is not functioning properly.

So what is the functional impact? Obviously, it varies from mild to severe. And at the mild stages of postanoxic encephalopathy, we have inattentiveness, weakening of judgment, and motor coordination. At a greater level of severity we have

memory impairments, apathy, disinhibition, and poor judgment.

And at the severest outcomes in postanoxic encephalopathy, in the otherwise awake patients, you have patients who have language disturbances, inability to recognize their environment, inability to use their hands in purposeful ways, amnestic disturbances, difficulty in calculations, and impaired reasoning.

In the physical spectrum, you have spasticity, paresis, ataxia, pseudobulbar palsy, and other kinds of effects there.

When we get down to this level of dysfunction -- and these are patients that I, unfortunately, have to see in my own clinical practice -- for such disabled individuals alive is not necessarily the better alternative.

Well, how do we know some of these outcomes? Well, in a study published by Roine and colleagues in JAMA about a decade ago, they looked at a placebo, controlled, randomized double-blind trial of nimodipine versus placebo, looking at 68 survivors

of out-of-hospital cardiac arrest who were evaluated over a two and a half year period.

And they took a look at neurocognitive outcomes in three and 12 months after discharge from the hospital. And by "neurocognitive outcome" I'm referring to functions such as language, memory, cognition, perception, and so forth.

They defined a priority -- a priori the abnormality as a score at or below the second percentile when compared to the normal population on that particular test, and what they found was the following. There was no statistical difference between nimodipine and placebo groups, which was bad news from the point of view of the clinical trial, but good news in the sense that we could collapse the groups and analyze the total outcomes.

The general intelligence scores were essentially within normal limits. There were no or mild deficits in about half of the survivors at one year. There was relatively mild impact on language and visual perception, and deficits were slightly less frequent at 12 months than they were at three months.

So from the point of view of people in the emergency room, these people were walking, they were talking, and at a very superficial level they seemed to be functioning well. But if you looked at the cognitive outcomes, half the patients had a moderate to severe abnormality in memory, manual dexterity, calculations, skilled motor movement, planning, initiation attention, motivation, and depression. And I'm going to come back to these Roine data later on in another context.

When you look at an MRI scan of a patient who suffered at a hospital cardiac arrest with memory intact versus impaired memory, it's not easily seen on the slide here, but if you compare these two slices of the brain -- and this is a front view of the brain where this is left, this is right, and this is the top, and this is the bottom -- you can see the increase in ventricular size. You see cortical loss here in the medial temple region, and you see here the sulcal enlargement.

So the point that was made here in this study was that the cardiac arrest is not a focal

problem; it's a whole brain problem.

Now, with all of this knowledge, it's kind of surprising that if you look at the emergency medical literature, most of their neurological outcomes have relied on something called the Cerebral Performance Categories, which I will describe briefly.

The highest level of performance, a good level of performance, involves patients who are conscious, alert, able to work, and lead a normal life. Then, we have minor psychological and neurological deficits. A moderate cerebral performance is a conscious patient who is capable of part-time work in a sheltered environment or independent activities of daily living, with some residual neurological deficits.

Severe cerebral performance are patients - involve patients who are conscious but fully dependent on others for their activities of daily living, coma and vegetative state, and down below there is death.

In most of the cardiac resuscitative literature, an intact neurological patient is one who falls into either of these two categories. And so the

question is: how sensitive are these measures to neurological function?

Well, if we take a look, first, at the highest level of outcome, of good cerebral performance, Hsu and her colleagues reported -- or discussed the fact that the CPC is subjective and its categories are poorly defined. It is frequently used only at hospital discharge, and it has never been validated or compared to other measures.

And so what they did was they compared the CPC with an instrument called the Functional Status Questionnaire at discharge and at followup, and the Functional Status Questionnaire is this well-validated study having been used in a variety of medical environments to take a look at patient outcomes.

And what they found was that a CPC score of one on discharge had a sensitivity of 78 percent, but a specificity of only 43 percent for same or better subjective quality of life than before the arrest. The ability of the CPC to predict abnormal performances on the Functional Status Questionnaire had a sensitivity of only 32 percent and specificity

of 43 percent.

And if you looked at the predictive ability of the CPC, the correlation of the CPC at discharge and at followup was only .32.

If you look now at the moderate cerebral performance category, this is now the part-time work. What I did was I took the liberty of taking a glance at the Social Security Act and what constituted someone who is eligible for disability benefits, and found under impaired organic mental disorders that the spheres of disability would occur in activities of daily living, social functioning, concentration, and deterioration in work and work settings.

If we now go back to the Roine data that I presented to you earlier, the 48 percent who have a moderate to severe impairment, they would be eligible for total and complete disability with a CPC score of two. Is this an attack neurological outcome? And I would suggest not.

So based on the existing evidence, the physical -- physiological, rather, of cerebral inoxia following cardiac arrest is well documented with

effects that can be both transient and permanent. And I can also tell you from my own clinical practice that even mild deficits can be permanent.

And, therefore, the teacher in the classroom or the attorney in court or the bond trader on Wall Street or the parent raising children -- a mild deficit can actually make a difference between competence and futility.

We need an objective, validated measure of brain function that will include physical and cognitive outcomes, and that these outcomes need to be specified in advance with operational definitions that take into consideration contemporary views of neurological function and imaging, and that the clinical performance scales lack the sensitivity and specificity needed to serve this role.

The measurement of brain function in a clinical trial should be performed by clinical neuroscience specialists who are blind to treatment, not the emergency room physician.

And, finally, neural endpoints need to be obtained in the acute period, at discharge, and at

longer term followup to ensure meaningful patient outcomes.

Thank you.

Okay. I'm now going to introduce Dr. Elisa Harvey, who will talk about exceptions in informed consent.

DR. HARVEY: Good morning. I'm Elisa Harvey. I'm representing the Investigational Device Exemption staff in ODE at FDA. And I'm here to provide a little bit of an overview regarding the regulations as they currently exist with respect to exception from informed consent for these kinds of device trials.

As we know, informed consent is a fundamental element of all human subject research, and these are outlined through the Declaration of Helsinki and the 1979 Belmont Report, which both identify the basic principles that are a part of informed consent.

It has long been recognized that there is an appropriate place for consent by a legally authorized representative or proxy for patients and populations that are incapable of providing their own

informed consent, such as the pediatric population or individuals that are cognitively impaired.

But prior to 1996, there was no mechanism in our regulations for prospectively waiving consent altogether for research. There were case-by-case waivers of consent but not a mechanism for a prospective waiver.

We recognize that there are obviously emergency situations where medical intervention is urgently needed, but the patient is unable to provide consent for whatever reason. And yet the urgency of the situation precludes obtaining consent by proxy, and, in particular, we recognize that research into this kind of area is also urgently needed.

So in order to try and address those issues, in 1996 a new FDA regulation was promulgated, not just for devices but at the agency level for all kinds of trials for emergency research where a waiver of consent might be an important element of the research.

And the regulation was intended to address this need to permit exception from informed consent in

very specific circumstances, which I'll go through. It recognized the need, though, that there should be some additional protections of patient's rights when research is undertaken in this fashion without consent.

The regulation was developed with significant input from the medical community through a series of open meetings, and also a draft regulation which was published in 1995 allowing for a comment period after which the final regulation was implemented in 1996.

The regulation is found here in the Code of Federal Regulations, 21 CFR 50.24. It identifies the specific criteria or circumstances for these kinds of studies and establishes the requirements for the study conduct. And it also identifies some additional steps that sponsors and IRBs must take to assure adequate patient protections.

The criteria are as follows. The subjects must be in a life-threatening situation. The current treatments that are available for treatment of that patient are both either unproven and/or

unsatisfactory. Participation in the study should hold at least the potential for direct benefit to that individual patient in that circumstance, not just an indirect benefit over the long term to a different population.

And the study could not feasibly be conducted without this exception. And what we mean by "feasibility" is that there would either be too few patients who would be able to provide the consent out of the total population in a study or who would have an acceptable proxy that would be available in the appropriate time period to provide that consent for them.

In addition, it wouldn't be -- the population must be such that it wouldn't be possible to prospectively identify the population from which those study patients would likely be drawn and able to provide consent ahead of time.

As far as the study conduct goes, the regulation stipulates that investigators must make every attempt to obtain consent from a legal or authorized representative within some specified --

within the protocol time interval before proceeding to go ahead and enter the patient in a study.

And if consent is not able to be gotten prospectively, the investigators must inform the patient and/or their legally authorized representative about their participation in the study as soon as possible.

The additional protections that are outlined in the regulation are that a separate IDE, or investigational device exemption application, must be submitted to and approved by the FDA ahead of time for all such studies. And the IRBs must consult -- this is an important aspect of it I know which has been the subject of much discussion, but IRBs must consult with the individual communities where this kind of study would be conducted.

The study must be publicly disclosed to those communities before initiation of the study, and the results must be publicly disclosed when the study is completed, either in the form of publications in peer review journals and potentially also in other venues that are more accessible to the lay population.

The study must be overseen by an Independent Data Safety Monitoring Board. And the IRBs for studies in which multiple study sites are involved must be notified of the concerns raised by other IRBs that are participating in that study, or approving that study.

In order to help assist in the clinical community in understanding what this regulation meant and how to appropriately meet the requirements, an FDA guidance document was issued in the year 2000. Again, this is not just for device trials, but for all kinds of studies involving unapproved products that would be a part of these kinds of emergency research trials.

The guidance can be found at this website, and what it does is attempt to clarify the requirements in the reg. And it was -- the content of the guidance has been informed by some of the initial experiences that were conducted under this reg following the 1996 publication. There was also a period of public comment for the draft guidance document, which identified the need for some further clarifications, and these clarifications and revisions

are currently underway.

As far as experience with the reg since it has been implemented in 1996, the most -- probably the one that's most cited is the Public Access Defibrillation trial, which was recently published in The New England Journal.

Some investigators have described their approaches to the regulatory requirements in detail, and I think these -- it's clear that these reports are very helpful in assisting the entire clinical community in developing approaches that are optimal for both the patients and the investigators in getting these studies done.

So as far as the current status of the regulation and these kinds of studies, the draft -- like I said, the draft guidance is currently being revised to incorporate some of the public comments and provide more clarification.

The past experience that has been out there thus far should facilitate some increased efficiency in some of the future studies that are done in accordance with these requirements. And we should

recognize that sponsors, investigators, IRBs, and FDA are all still in learning mode with respect to how to best implement this regulation and make sure we're providing adequate patient protections.

If there are any questions or comments about the regulation or the guidance, I'd be happy to take questions, either now or following the meeting. I can be reached by e-mail or phone, and I'd be happy to take the questions.

Thank you.

And I guess Geretta is going to -- or Geretta is going to read the questions?

ACTING CHAIRPERSON MAISEL: We'll do the questions later. So I'd like to thank the FDA for their presentation and for providing an excellent foundation for this morning's discussion, and at this point invite the Panel to ask any questions of the FDA, reminding, of course, the Panel that they will have ample opportunity to discuss these issues later.

Yes, Dr. Brott.

DR. BROTT: Dr. Lazar's group at Columbia has a long history of investigation of patients'

cognitive function in association with brain injury, particularly with stroke. And I'm wondering if Dr. Lazar could make some suggestions on what neurological endpoints he would either recommend or recommend for study.

DR. LAZAR: I think that's a good question, and I think that, for example, having a neurological physical outcome scales, like the NIH Stroke Scale, for example. Let's separate the physical and the cognitive outcomes. I think that for physical outcomes we can look at things like the NIH Stroke Scale, for example, which has more quantitation than merely observation of what people can do.

I also think that scales like the Barthel and the Modified Rankin Scale can also be used to measure some aspects of the impact of physical disability. With regard to cognitive outcomes, as you know, being a stroke neurologist, that it takes longer to evaluate that. And I think that we could target the nature of the test to the kinds of dysfunction we would expect.

So that there has to be measurement of

memory and language and psychomotor speed, and so forth, and that there are really I think well-recognized tests that can be used in a reasonable amount of time to measure these outcomes. It doesn't have to be a five-hour battery of neurocognitive tests. They can be done in a much shorter interval than that. If you want names of specific tests, we can do that also, but I'm not sure this is the venue for that.

Did I answer your question for you?

DR. BROTT: Yes.

ACTING CHAIRPERSON MAISEL: Dr. Yancy.

DR. SOMBERG: I just wanted to followup. Do you have one for him? No.

If you -- you sort of -- well, you didn't sort of, you did suggest that the CPC test was inadequate, both in sensitivity and specificity. Could you be specific about what is adequate?

DR. LAZAR: I think that what is adequate is that it's not only what you test, it's also when you test it. And typically the CPC is used at the time of discharge, and there are not many published

studies on long-term outcomes with the CPC. And the CPC was never validated against other measurements.

So it would mean that at the time that the patient is admitted that a neurologist, for example, would do an initial thorough neurologic exam and put that into something like the NIH Stroke Scale, or something like that, to measure neurological disability. Cognitive function is not necessarily assessable at that point in time.

As you get to discharge, you repeat the neurological exam with an outcome measure like the NIH Stroke Scale, and then you use measures of word retrieval and of memory and of perception, and so forth, that could be used, let's say, at discharge. And a battery of tests can be anywhere from 45 minutes to an hour, to measure those outcomes. Some patients will do well on them, and some patients will not.

And then, you can measure them in 30 days, and then you can measure them at six months and at one year, and, therefore, get serial measurement of these functions over time. You could also look at other outcomes such as -- of cerebral blood flow. You could

look at Doppler. You could look at diffusion-weighted MRI, which I -- data I didn't present, as surrogate measures of neurological outcome.

DR. SOMBERG: I would just say that, you know, I hear what you're saying, but in a clinical trial you want to maintain -- you want to be effective, but you also want to be simple. And you seem to be implying that there's no simple instrument. Having a neurologist spend an hour two or three times with each patient makes --

DR. LAZAR: Well, I --

DR. SOMBERG: -- makes for greater complexity.

DR. LAZAR: Well, I think you're right. Unfortunately, the brain is not a simple organ. And it does -- it does a lot of things, and it -- we have physical outcomes, we have cognitive outcomes, and if -- and you also have to think about the burden to the patient having incurred a cardiac arrest and what happens to them outside and what the costs are to them.

There may be costs of testing these

functions, but there's also a cost to patients who are struggling out there who are led to believe that they're surviving well when, in fact, they're not. And I think we need to know what it is that happens to them as a result of intervention, and it's something that's not approached in a trivial kind of way.

DR. ZUCKERMAN: Dr. Somberg, your points are well taken. But I would make the analogy to what we found, for example, with the LVAD development program, where neurological function is a key aspect of the effectiveness that we're trying to determine here.

Again, the key concept is to make the neurological testing user-friendly, and we do abide by those principles. But I do think in terms of the overall effectiveness question we can't forget about Dr. Lazar's points, and certainly we have great neurological input here today.

ACTING CHAIRPERSON MAISEL: Dr. Yancy.

DR. YANCY: Along a different line of questioning for the FDA, I was struck to see over 30 devices that have an approval for the indication for

CPR. And I'm wondering if there's any post-marketing data on the outcomes, since those devices have been approved.

In large measure, the methodology is woefully unacceptable, and I would think that we would have some rationale to continue to collect data to see if a learning curve is present, so that outcomes are better, or, if as it's widely distributed, the results are even less good because the operator variability increases.

Are there any post-marketing data?

MS. TRITSCHLER: The short answer is no. And a little bit of explanation along with that is the 30 cleared devices are cleared and not approved. They're cleared through the 510(k) process, and that's different from the PMA process. So we don't have the same ability to request a post-approval study.

DR. YANCY: So how many devices are on the market? Or maybe some of our emergency consultants can tell us that. How many devices --

MS. TRITSCHLER: I'm sorry. How many of which type of device?

DR. YANCY: How many of the resuscitation devices are actually on the market and being utilized?

MS. TRITSCHLER: There's about -- probably about 40 total that have 510(k) clearance. I don't know how many are currently marketed, and those devices that have the 510(k) clearance are just intended to assist the rescuer. They aren't intended to enhance any kind of clinical outcome of CPR.

Does that answer --

DR. YANCY: That does. But I think that one of the things we should consider in any trial design is the requirement for ongoing longitudinal data collection.

ACTING CHAIRPERSON MAISEL: Dr. Brinker.

DR. BRINKER: I was wondering about your category of those CPR devices that bring about hemodynamic improvement. It seems to me that you're not only looking for hemodynamic improvement, because hemodynamic improvement, at least during CPR, would be easily surrogated to relatively simply measured entities.

But what you're really looking for is an

endpoint to the hemodynamic improvement. So at the end of the day, aren't you always looking for better survival as a final common denominator rather than hemodynamic improvement during the application of the device?

DR. ZUCKERMAN: Perhaps. I think that's one of the reasons why this Panel has convened. CPR trials, for a variety of reasons, are extremely difficult to perform, and this Panel will deliberate on many aspects of trial design.

But, you know, certainly in an ideal world, perhaps we would like to be able to point to a surrogate that would both correlate and fully capture the endpoint of interest, which you've mentioned, Dr. Brinker.

The real question, though, is: is there a surrogate for the one you've mentioned, or even some endpoint that comes close that could be utilized for trial design in this field?

DR. BRINKER: So, Bram, let's say I had a device that could unequivocally, during CPR, give me higher blood pressure, greater cardiac output, and

perhaps even -- well, let's stop there. But as a subcategory, perhaps increase cerebral blood flow.

And I studied this device, and I confirmed all those observations, yet there was no increase in survival to hospital -- end of hospitalization, nor neurologically intact survival. Would that device be approved as a -- because it could deliver hemodynamic improvement over other available devices?

ACTING CHAIRPERSON MAISEL: I'm going to interrupt and simply comment that we'll have plenty of time to discuss the appropriate endpoints and whether -- you know, we can decide what the appropriate endpoints are.

Dr. Normand, did you have a question?

DR. NORMAND: Yes, I have a question completely unrelated to that. I was wondering if the FDA could comment on the issues with the studies conducted outside the U.S. And, specifically, you mentioned variations in EMS, and I am wondering whether or not data could be collected that one could adjust for such differences and things of that nature.

DR. HARVEY: Well, I'm not sure I

specifically can answer that question, but I did want to make a clarification about two aspects of the regulation that I didn't mention before. One has to do with the acceptability of OUS data when it hasn't explicitly followed the U.S. regulation.

And the answer to the question of whether that kind of data would be acceptable is that it's not obligated to follow the reg, since it's conducted outside the country. What it is obligated to do is follow either that individual country's regulations and laws, or the Declaration of Helsinki, whichever affords the greater protections.

The other clarification I wanted to make had to do with how pediatric populations in studies are intended to be included or not in -- within the context of this reg. And they're not specifically addressed in this Reg 50.24, but they're not excluded either. We recognize that a large number of these studies might potentially involve pediatric populations, and they are intended to be a part of this regulation as well.

Pediatric consent and research is also

covered a little further down in that regulation in 50.55. And they don't supersede or trump one another; both of those parts of the regulation should be followed with respect to pediatric consent.

DR. NORMAND: But if I --

DR. HARVEY: As far as the rest of your question, probably somebody else is better suited to answer that.

DR. ZUCKERMAN: Dr. Normand, so I think, if I interpret your question correctly, if we do operate within the regs, can we do a global CPR trial?

DR. NORMAND: Yes. In other words --

DR. ZUCKERMAN: Yes.

DR. NORMAND: -- yes.

DR. ZUCKERMAN: Okay. And the answer is: perhaps. Certainly, when we look at outside U.S. data, even when it is collected within our -- the proper regulatory framework for OUS data, we want to make sure that the data can be extrapolated to the American population.

The FDA presenters gave one example where we had trouble making that extrapolation in this

particular device field, and we've had other examples in other device fields. However, I do think if one prospectively considers the appropriate questions, as you seem to be doing, then the potential is there for more of a global drop.

ACTING CHAIRPERSON MAISEL: Dr. Somberg.

DR. SOMBERG: Well, just specifically about this point, you bring up one of the problems of the regulations, in that the Declaration of Helsinki, to my understanding and from what I've been told in this area, does not provide for investigation without informed consent.

So since that is considered the highest form of protection outside the U.S., there's really not a provision for this type of investigation, as I see it. It is often done, but truly there isn't -- unless you tell me that's been changed in some wy.

DR. HARVEY: Well, duly noted. I mean, this is the regulation as it currently exists. It's my understanding that there are currently efforts or activities underway at the agency to relook at how we express our interest in what kinds of patient

protections are afforded in studies that are done OUS, and it may be that we are going to approach it from a different perspective than just the Declaration of Helsinki in the future. But these are the circumstances we have right now, so --

ACTING CHAIRPERSON MAISEL: Dr. Halperin.

DR. HALPERIN: Yes. I --

DR. BROCKMAN: Can I just make a -- can I make a comment? I'm sorry. Bram alluded to the comment I'm going to make, but in dealing with the OUS data -- this is going back to one of the points I made.

We occasionally have trouble taking OUS data when the EMS system in the region of interest is substantially different from the EMS system here, and the example I cited was a study by Plaisance where a physician was present on the scene of all outside hospital arrests. They respond with the EMS system, so a physician -- a critical care or emergency specialist was present to guide ACLS therapy on the scene.

Well, so was the improvement in survival

due to the fact that there was a physician on the scene? Or was it due to the device? We just don't know the answer to that, and it's difficult to port that, then, into our EMS system here.

DR. NORMAND: My question was more in the spirit of prospectively, if -- I just wanted to understand, if it's retrospectively, it's not fixable. But prospectively, if --

ACTING CHAIRPERSON MAISEL: Dr. Halperin.

DR. HALPERIN: Yes. I'd just like a clarification on regulations versus science, and the way this -- one of the devices are classified, because, in fact, there's apparently 30 or 40 devices that have been approved to -- as external cardiac compressors or aids in external cardiac compression, but none have been improved for improving hemodynamics.

But, in fact, it's been well documented that properly performed CPR generates substantially better hemodynamics than improperly performed CPR. I mean, this is from many different laboratories.

So, in fact, then, devices that assure the

correct performance of CPR are, in fact, improving the hemodynamics. But yet if one claims apparently that a device is being approved for improved hemodynamics, then that's a different process.

Can clarification be made about that?

MS. FLEISCHER: Just for the record, I'm Dina Fleischer from the FDA. Yes. I don't want to get into a big discussion on the difference between 510(k) and PMA. However, when it's a 510(k), you're basically saying you're equivalent to something already cleared on the market.

And so the claims that are being made would have to be the same indication for use in sort of the same sort of claims. And so that's why they sort of -- those 30 devices all are -- are aids in CPR.

Now, if the claim that you want to make with their device, for instance, is that it improves the hemodynamics, etcetera, that would be a new indication for use. Now, what route that would take hasn't been -- we haven't really clearly defined in FDA.

But just to say that it is a new indication, and so it would be different data that would need to be provided, perhaps a PMA with an IDE, and that's a route that can be taken. But up until now, the data that we've given you is what has been submitted to the FDA, and the data that has been submitted.

Is that clear, or --

DR. HALPERIN: There still seems to be a disconnect between the science and the regulations in that respect.

MS. FLEISCHER: That's why we're hoping that this Panel will help us sort of streamline the process and get clearer points for the indications for use.

ACTING CHAIRPERSON MAISEL: Dr. Marler, and then Dr. Becker.

DR. MARLER: Yes. I wanted to ask the FDA about more specific information about the timing of two processes. I guess one is: how long can it be before the heart is essentially restarted or CPR is started? How long does the brain survive? And how

long do you have to perform an intervention? To me, it seems to be a critical time.

And then, how many patients are in trials of devices that actually are within the time that the brain actually can respond to any treatment before that infarction is the predominant place where it is? Because it seems to me you have two independent processes, and we're not directly thinking about it and hooking them together. But you'd have to start the recirculation in a time that the brain can respond.

In other words, what was the time scale on your -- on the slide? And what was the time scale on the trials that have been done?

DR. LAZAR: I don't have an answer on the trials that were done, because most of the -- most of the more in-depth studies are not done right at that moment when they're admitted. Most patients, as you know, don't survive.

I think it's about four to six minutes following the cardiac arrest when the brain really begins to fail. And there are other factors, as you

know, that impact upon that -- the age of the patient, how much, you know, intercranial disease might already exist, and so forth. So it's a very, very brief interval, and --

DR. MARLER: So if you don't get some blood-carrying oxygen and glucose to the brain within four to six minutes, you're not likely to have much impact on neurological outcome, is that correct?

DR. LAZAR: Not much beyond that. That's to my knowledge. Those are the studies that I'm aware of.

DR. MARLER: It seems to me that clears a lot of the air, but --

ACTING CHAIRPERSON MAISEL: Did you have a comment on -- Dr. Weisfeldt, did you have a comment on this?

DR. WEISFELDT: Well, Dr. Lazar, just I'm concerned about the lack of control for the nimodipine placebo data. I'm concerned not only about age adjustment but disease adjustment. Patients who undergo cardiac arrest clearly have cardiovascular disease that often affects brain function itself. Can

you give us any notion about what a disease- and age-adjusted population might show in the same testing?

DR. LAZAR: I don't have a good answer for that, and the studies that I've read haven't explored that in depth. I mean, one of the things is -- well, let's say the patient had a stroke prior to the cardiac arrest. What would be the implication for that patient, for example? And so in some of the literature that make a distinction between the CPC, and then there's another scale that tries to factor in how the patient was functioning prior to the cardiac arrest.

And they've tried to do some interviewing of a patient who was in a nursing home, for example, or living independently at home, and so forth, and trying to factor that in. But there the outcomes have always been the CPC and nothing more fine-grained.

And so we really don't have the answers to the questions that you're really asking, but I think they're very important ones.

DR. MARLER: So there's no answer to me on the time interval for patients in existing trials?

DR. LAZAR: That's correct. To my knowledge, with -- with fine-grain measurement, that would satisfy conventional neurologic criteria.

ACTING CHAIRPERSON MAISEL: Any other burning questions for the FDA before we move on? Why don't we -- we'll take two more questions -- Dr. Becker and Dr. Hallstrom -- and then we'll move on.

DR. BECKER: Yes. I'd like to thank the Panel, and I'd like to ask the question in terms of can you give us a little more explicit information in terms of labeling? We've heard about device categorization, but isn't labeling and the request for labeling from a sponsor an important piece of the burden, if you will, that needs to be presented?

And so my question is: as you talked about the different generations of devices with -- it was quite notable that sort of the third generation has almost no approved device at this point. Could you comment on whether that's really a labeling issue, meaning the claim of superiority, or is that something intrinsic to the device itself?

MS. TRITSCHLER: I don't think that it's

really a labeling issue. The FDA kind of made a regulatory decision that devices that have this ability or capacity to enhance clinical outcomes, even if they're not going to label that claim, if they have the ability to do that, they still need to have clinical data to support that.

DR. BECKER: But so just to clarify, so if a device that improved hemodynamics, for example, said that it simply was equivalent to standard CPR, would the burden of science based on that be different than, you know, a much lesser device that would make the same claim?

DR. ZUCKERMAN: Okay. Those are very important and difficult questions to answer, and that's why we have a whole question set. But I think what you're getting at, Dr. Becker, is an important point, in that the third-generation devices have looked for a superiority claim. And you're suggesting, could the agency consider an equivalence claim?

We're looking to the Panel experts to help us out on that particular question, and we're very

interested in hearing your responses, number one. So I'm not going to bias the Panel.

But, number two, I think it will be very important to hear from the Panel members and our statisticians as to what an equivalence claim actually implies, etcetera. Sometimes equivalence trials are harder to do than superiority trials.

ACTING CHAIRPERSON MAISEL: Dr. Hallstrom?

DR. HALLSTROM: Yes, I had a question again for Dr. Lazar. I'm sorry I didn't get it in there when you were standing up. I'm concerned about what you're doing with missing data when you have these repeated measures long term. You're going to have a substantial amount of dropout and refusals.

DR. LAZAR: You're absolutely right, and how we deal with the missing data is an important statistical matter. I know that when I was working with Sharon-Lise on heart failure, and looking at LVADs and other mechanical circulatory support, this same matter came up. And it's a very complex statistical issue, and we need statisticians to help us. But perhaps we could take a look at the

characteristics of the patients up until the time that they're lost. That's certainly one starting point.

And to see whether or not there are any predictive factors about who it is that drops out of the system, and to see whether or not that is analytically helpful to us. But I appreciate your point, and the survival analysis is very complicated in dealing with the dropouts. I understand your point.

ACTING CHAIRPERSON MAISEL: Thank you.

I'd like to move on at this point. We'll have opportunity to discuss these issues further and to question the FDA, if desired, later. At this point, I'd like to open the public hearing session of the meeting. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making.

To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product -- we don't have a sponsor today, but products, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any financial -- such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So at this point, I'd like to call the first speaker, Kenneth Collins, to the podium.

MR. COLLINS: Good morning. My name is Kenneth Collins. I'm the Executive Vice President at Alsius Corporation. I'm a full-time employee. They're my financial interest.

Alsius is a manufacturer of medical devices, including devices marketed currently in the United States for fever reduction and for the induction, maintenance, and reversal of mild hypothermia, in specific patient populations not under discussion today.

Alsius does have before the FDA a 510(k) notification pending for clearance that relates to an existing marketed endovascular heat exchange system for use in the induction, maintenance, and reversal of mild hypothermia, in the treatment of adult patients after out-of-hospital cardiac arrest where the initial rhythm was ventricular fibrillation.

As stated in the FDA's Register notice, we're here to discuss and make recommendations regarding clinical trial design and the evaluation of CPR-enhancing devices and therapies for cardiac arrest patients.

As a manufacturer of medical devices, we have sought to present today, relating specifically to the session this afternoon on hypothermia in the post-recovery phase of resuscitation care. Cardiac arrest

is not, in itself, a disease. It's a potentially reversal plunge from life to death.

Successful resuscitation returns the patient to life, but there are consequences to face in connection with the treatment and outcomes of the precipitating disease state, and the additional effects of the hypoxic insult associated with the arrest.

Successful treatment of sudden cardiac arrest, its predecessor conditions, and sequelae, requires interventions applied across multiple providers, often across several clinical settings -- the so-called chain of life.

These interventions make it difficult to assess the contribution of any single link in the chain. Even so, multiple interventions, including hypothermia, have been subject to complex multi-year trials and have been shown to be effective in reproving morbidity and/or mortality in this devastating state.

The focus of the comments today from -- my comments today are on therapeutic hypothermia,

controlled or mild hypothermia, and sudden cardiac arrest.

This has been a topic for nearly 50 years. There is now persuasive data demonstrating the benefit in humans. In fact, the therapeutic value of hypothermia in the immediate treatment of the patient suffering out-of-hospital cardiac arrest has been recognized and included in professional guidelines.

The American Heart Association, American College of Cardiology, as part of their membership in the International Liaison Committee on Resuscitation, have recommended that the unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32 to 34 degrees for 12 to 24 hours when the initial rhythm was ventricular fibrillation.

This recommendation is based upon two randomized controlled trials -- the so-called HACA, or Hypothermia After Cardiac Arrest study in Europe, and the study by Bernard, et al. in Australia.

Significant improvements in morbidity and mortality were obtained. If you look at the data as a

whole, if you treat seven patients, an additional one goes home, there are several methods for inducing mild hypothermia achieved in the HACA and Bernard clinical trials.

External means, such as ice packs, cold blankets, and forced-air cooling have been most commonly used to date. Other methods of inducing comparable hypothermia are variable, including endovascular heat exchange catheters. These products are already released and on the market for other indications, for uses that include both normothermia applications but also the induction, maintenance, and reversal of mild hypothermia.

Each of these devices serves as a tool for inducing mild hypothermia. Alsius believes that in the light of the pre-clinical and clinical data already available there is no reasonable, scientific basis to require each individual device to bear the full burden of another randomized controlled trial to prove the clinical utility of inducing mild hypothermia in sudden cardiac arrest patients.

I'm being told to sum up.

The question to the FDA review of individual devices in this particular setting should not be whether each individual device can, once again, be shown to improve survival, but, rather, where the device introduces new questions of safety or efficacy that are different from the predicate devices.

If the clinical data are required, the FDA and the sponsor can and should be feasible in choosing the most appropriate data types and study methods consistent with the statutory least burdensome approach. The FDA has shown clear leadership in its use of post-market studies.

I do wish to press one small point made by a previous speaker. The FDA does issue post-market surveillance orders in relation to 510(k) product. Indeed, it has recently done so in respect to temperature regulation devices.

The ability to use post-market studies after clearance, in conjunction with such agencies as the National Registry of Cardiopulmonary Resuscitation, offers real public value, particularly since there are provisions within the Hospital

Insurance Portability and Accountability Act that allow efficient data collection under the FDA's tight and appropriate oversight.

Thank you for allowing the presentation.

ACTING CHAIRPERSON MAISEL: Thank you.

The next speaker is Dr. Keith Lurie.

DR. LURIE: Good morning. My name is Keith Lurie. I am a practicing cardiac electrophysiologist, an inventor of the active compression-decompression, and co-inventor of the impedance threshold device. And I founded a company, Advanced Circulatory Systems, to try to get this technology onto the streets.

I'm also a professor of medicine and emergency medicine at the University of Minnesota, and I'm pleased to be able to speak to this committee this morning.

I'd really like to thank you, the FDA, for having this Panel meeting today. It's a very important step in helping to evaluate new CPR technologies.

Despite the widespread practice of CPR,

its inherent inefficiencies contribute to the extraordinarily high death rates for patients with cardiac arrest. Greater than 1,000 Americans will die today from cardiac arrest. That's more than all the losses of Americans in Iraq to date. Half of those patients, or less actually, present with ventricular fibrillation, the most favorable rhythm we've heard about.

And even after surviving to the hospital, nearly 75 percent of them will die before hospital discharge. This problem is enormous. It's been underrecognized, and it must be recognized before this Panel can logically proceed with ways to look at the questions at hand.

We are very pleased that the FDA is taking a fresh look at this problem of CPR device evaluation.

My first point relates to the need to define minimal essential requirements for safety and effectiveness of new CPR devices. Safety and effectiveness, as this is a disease process where nearly all people die, are certainly relative.

Even in cities like Seattle, survival

rates are only 17 percent for all patients who receive CPR. We can do better. By defining the essential minimal requirements for safety and efficacy for CPR devices, by using the current standard of care, a pair of hands for comparison, we will make a big step forward. Very few people use those 30-plus cleared devices that we heard about.

My second and most important point focuses on the question of endpoints for studies of new CPR technology. They must be consistent with the chain of survival approach recommended by the experts at the AHA. Each new technology should only be evaluated foremost to demonstrate safety and effectiveness for what it was designed to do.

For example, if a defibrillator is being developed to terminate ventricular fibrillation, and studies show that it can safely and effectively accomplish this task, such studies should be sufficient for a new device clearance.

Given the non-standardized care of patients once they are admitted to the hospital, it is difficult, if not impossible at present, to control

for the large number of critical variables associated within hospital care that impact the potential value of a CPR device.

What is, therefore, critically needed is that each device that strengthens each link in the chain of survival is evaluated by itself to make sure that it is able to safely and effectively strengthen that given link in the chain, whether it's an improved way to call for help, whether it's an improved way to move blood during CPR, to ventilate and provide oxygen without lowering blood pressure, to defibrillate at the right time with the right kind of energy without damaging the heart, or to provide cooling.

Each new technology must be evaluated to determine if it is as safe and effective as whatever is being used today. If the standard of care is a pair of hands, that should be the standard to which the alternative therapies will be tested. Not some other device or technology that either does not work or is no longer being used in the care of patients.

We all strive for longer-term patient outcomes, such as increased hospital discharge or one-

year survival. However, if such endpoints are required prior to the initial clearance of new CPR technologies that were developed to strengthen each individual link in the chain of survival, there will be little or no progress.

For example, no biphasic defibrillator has ever been shown to improve long-term survival. But such devices are the standard of care as they defibrillate more effectively than earlier versions.

Demanding long-term endpoints prior to clearing products for use would be unfair to the technology, deny care to the patients who desperately need them. And, moreover, the long-term survival endpoints cannot be achievable without an enormous number of patients, large, more adequately powered studies, not to mention the tremendous expense, and, most importantly, the opportunity cost in terms of the lives lost along the way prior to the device clearance.

If we use AEDs as an example, they were introduced in the mid-'80s in Seattle by Dr. Leonard Cobb. Twenty years later, $25 million later, and with

a barely statistically significant study, The New England Journal most recently described the results of the PAD trial by members of this Panel. That's a great trial, but think of all the lives that would have been lost had we not had the AEDs out there in advance.

My final and third point is that the control group is critical for CPR studies. The control group study should be the current standard of care recommended by the AHA. Technologies and approaches that are speculative and not based on conclusive results with patients should not serve as a control. The gold standard for CPR is conventional manual CPR, not a device. Conventional CPR should serve as a control group until there is another gold standard.

We are at a crossroads in CPR research. To impact the extraordinarily high current mortality rates, it would require more rapid, nimble, and creative thinking about this technology, a lowering of regulatory barriers, and a commitment by all parties involved to remain engaged in developing and testing

these new technologies.

The FDA can continue to play a leadership role by first recognizing the regulatory barriers, that they have prevented progress, and, second, developing creative ways to remove these barriers. This meeting is a real step forward in this regard.

While I praise the recent efforts of the FDA to, for example, allow defibrillators to be sold without prescription, there will be no real progress in CPR until we move more blood.

MS. WOOD: Please, please complete your statement.

DR. LURIE: I shall. Thank you. Until we move more blood during CPR. Many of the devices that strengthen the links in the chain of survival are already developed. With an improved understanding of what is needed to demonstrate their safety and effectiveness in clinical trials, we can pick the right road forward, so that our loved ones, our friends, our neighbors, really have a second chance after cardiac arrest.

Thank you.

ACTING CHAIRPERSON MAISEL: Thank you.

The next speaker is Dr. Joe Putnam. Is Dr. Putnam here? Is there another representative of the Society of Thoracic Surgeons here? Okay. Very well.

Geretta will now read a statement into the record.

MS. WOOD: This letter is dated September 6, 2004. "Thank you for this opportunity to address you. I would like to make a few comments about both the need to develop and implement studies of new devices for the treatment of sudden out-of-hospital cardiac arrest, OOHCA, and the ethical challenges related to conducting these studies.

"Primarily, this is a plea to further study the process of protecting human subjects while moving forward with well-designed studies. Of course, sound science is an integral part of protecting subjects, since it is only reasonable to ask subjects to accept the possible risks of a study if there is real hope that the study will provide the answers to a scientific question that will then benefit future

patients.

"It is estimated that between 250- to 450,000 Americans over the age of 35 die from sudden cardiac death annually. Despite advances in health care, there has been little improvement in survival from OOHCA, which is estimated to be 5 percent nationally. In fact, the proportion of cardiac deaths attributable to OOHCA increased by 23.5 percent between 1989 and 1998. Thus, well-designed studies testing new treatment interventions in cardiac arrest are critical.

"However, for treatments to be effective, they must be administered early. This often makes it impossible to obtain informed consent from the patients before enrolling them in the studies of new, potentially beneficial treatments. Surrogates are not commonly available at the scene, and when they are the emotional nature of the situation often makes obtaining consent from them impossible.

"This dilemma can be summarized as: consent of human subjects for participation in research requires that they fully understand their

role and risk, not be coerced, and be allowed to withdraw at any time without penalty.

"In an emergency situation, informed consent is not always possible, but the need for good research data is very high. Here is the ethnical difficulty and a real conflict of values. A population that might ultimately benefit from research cannot consent to the research, and are, thus, excluded from the potential of therapeutic advances.

"Patients at high risk of morbidity or death with cardiac arrest, shock, head injury, or altered mental status are evidently incapable of providing an adequate consent, but, nevertheless, are often in the greatest need of innovative therapy and might be willing to assume some risk for potential benefit.

"To help address this dilemma, in 1996 the Department of Health and Human Services and the Food and Drug Administration jointly published regulations known as the Final Rule for performing studies when obtaining prospective informed consent is impossible because of the patient's acute medical condition.

"These regulations create two new safeguards to protect human subjects -- community consultation and community notification. Limited information is known about the effectiveness of the community consultation and notification process.

"Researchers have raised concerns that the rules hinder their ability to perform resuscitation research. At the same time, there is also little known about subjects' actual experience in these studies, and whether they are adequately protected. While studies using these rules have the potential to find new treatments that may save lives, the burdens and risks of these studies fall to the subjects enrolled in the studies.

"While challenging studies have successfully used exception to informed consent, a recent abstract reporting on a survey of United States medical school IRBs found that a significant number of IRBs at medical schools have reviewed at least one study under the final rule, and that the more funding a site receives from NIH the more likely it is to have reviewed a study.

"On the other hand, another recent study suggests that the new rules may be limiting the ability of United States researchers to perform resuscitation research. They found a decrease in cardiac arrest trials in the past decade and suggest that this may be due to the regulations.

"Surveys of public willingness to be involved in research without consent has shown that willingness depended on income and the perceived risk of harm. These studies also found many respondents had concerns about studies performed without consent, but most subjects would personally be willing to be enrolled in such a study.

"No studies to date have evaluated the experience of subjects that have been enrolled in a study using exception to informed consent. We do not know whether or not these subjects believe that the process protected their rights. Such studies may help determine better means of community consultation and notification.

"We do know that researchers report that complying with the rules is complex. For example, the

public access to defibrillation trial, PAD trial, found that the study was reviewed by a total of 101 IRBs, and median interval from submission to approval was 108 days.

"They were unable to report on total cost, because this data was not collected prospectively. One study found that the disclosure process required in excess of 80 hours. Another found that the process leading to waiver added $5,600 to a study that was terminated after four persons were enrolled.

"Calls have been made for modifications to the statutes. However, those who advocate rewriting the regulations most carefully assess what the -- must carefully assess what the real barriers to resuscitation research are.

"A lack of understanding of the regulations may exist, and the final rule was not written to make research without consent easy, but to protect patients. As the dialogue continues, and as we learn more, the time may come to approach you, the policymakers, to modify the laws.

"However, before that can or should

happen, we need objective data about how the rules are affecting both the ability to perform the research and the subjects they are meant to protect. If the guidelines are to continue, there is a need to determine if patients enrolled in such studies believe that their rights have been protected.

"At the present, we need to look for novel ways to implement the rules. A study of 16 IRBs from the institutions participating in a multi-center trial found variability in several areas. One IRB waived the requirement for informed consent, five IRBs permitted telephone consent, and three IRBs allowed prisoners to be enrolled.

"Because multi-center trials require the approval of so many IRBs, some have suggested the establishment of a central IRB. Such an IRB could be composed of ethicists with expertise in the regulations surrounding exemption from informed consent research, resuscitation researchers, and a diverse spectrum of community representatives.

"Thank you for your time. Terri Schmidt, M.D., M.S., Professor and Vice Chair, Department of

Emergency Medicine, Oregon Health and Sciences University, Chair, Ethics Committee, Society for Academic Emergency Medicine.

ACTING CHAIRPERSON MAISEL: Thank you, Geretta.

Is there anyone else in the audience that wishes to address the Panel today on today's topic or any other topic? Seeing none, at this point I would like to close the open public hearing.

It is now -- I have 10:40. Why don't we take a 15-minute break and reconvene at 10:55.

(Whereupon, the proceedings in the foregoing matter went off the record at 10:40 a.m. and went back on the record at 10:58 a.m.)

ACTING CHAIRPERSON MAISEL: So we'll begin our open committee discussion at this point, and we will use the FDA questions as a guide. There are three main topics, maybe four, within the FDA questions. And what we'll do is discuss each topic and try to confine our comments to the topic at hand, and then answer the questions.

So, for example, the first one is inclusion/exclusion criteria for the CPR-enhancing devices. And so why don't we open the discussion on who should be included in these trials, you know, witness/non-witness arrests, type of rhythm -- VF or other rhythms -- etcetera. So why don't we have discussion on those topics.

Joe.

DR. ORNATO: Thank you for giving us all an opportunity to put our minds together. Specials thanks to the FDA.

In response to your question, I think it really, to some extent, of course depends on precisely what you're looking at for a device or a drug. If you're looking at biphasic versus monophasic, for example, obviously you're just going to be looking at VF patients.

That said, I think for many of the broader trials, unless there's some specific niche that's being targeted, as in the defibrillator issue, it's awfully difficult to really be sure what rhythm you're dealing with initially.

Now, if it's clearly pulseless electrical activity, and you've unorganized rhythm but no pulse, no signs of life, that's fairly easy. But the differentiation between coarse, medium, fine, particularly fine VF, and asystole, is very, very murky.

And in our EMS system -- I'm Medical Director for the City of Richmond -- we regularly show our paramedics tracings that they've recorded from the field with five- or 10-second snippets of rhythm. And they will raise their hand, how many think it's V-fib, how many think it's fine V-fib, how many think it's asystole.

And what I'm getting at is they'll disagree, we'll have sort of a bell-shaped curve. We'll show the next rhythm. They don't realize they're coming from contiguous five- to 10-second strips of the exact same patient. Because VF has a direction, has a vector, it's very difficult to know in any tiny snippet whether you're really dealing with VF or you're just 90 degrees off the vector.

So I think most of us are becoming more

convinced that the rhythm itself initially is maybe a little less important. And it's a lot easier to design trials when you throw out the broad net and take all the rest, or at least all the rest that are witnessed, where you've got some belief that it's been a relatively short downtime interval, and then do you subanalyses afterwards.

It gets you out of a lot of the problematic areas, again with the exception of interventions that are very specific to the rhythm, like ventricular failure.

Hopefully, that will get us started.

ACTING CHAIRPERSON MAISEL: Dr. Somberg.

DR. SOMBERG: Well, I hear what Dr. Ornato says, and I have a concern in that, yes, the rhythm may not be the most critical aspect, except it depends on what device you're developing, of course, if it has a relation directly to conversion of a rhythm.

But isn't a rhythm a good surrogate for time down? And, I mean, you know, it's a classic thing. You run to an arrest. The only experience I have is the hospitals. If you run into arrest in a

hospital, you turn around and you say -- you know, four walls, "How long has this patient been down?"

If you don't get an answer, or if, you know, you have an assistant or some nurse's aid, or what have you, they discover this. I mean, they just look and say, you know, "This happened." So, therefore, I think it -- you know, if you have ventricular fibrillation, not always, but it may be more likely that you have a latency that's diminished.

And I think one -- you know, there are several key considerations in our discussion today, and I think the first one is the latency. And that is the time from the initial occurrence to when you lose perfusion, and I think that relates to a lot of determinants of outcome. And if you have a very long period, I'm not sure there's anything you're going to do.

In fact, we heard this four to six minutes. Let's say that's true. Let's say six minutes, or we'll give it eight minutes. That means most cardiac arrests in the United States cannot be addressed effectively, because no one is going to get

to people in six or eight minutes. I mean, you know, if we drove out here, went to 270 and back, it would take longer. So I don't know how an ambulance could possibly get to someone.

So with all that said, I think the rhythm may not be -- you know, we don't want to approve a device for hemodynamic CPR augmentation because you have VF, fine VF, tosade de pointes, you know, multi-form ventricular tachycardia, etcetera. But it may be an index.

And if I was doing a study -- I mean, you know, all of these are going to be recommendations to someone who is sitting there, the Panel to set up a study, but if I was doing a study, I would want to pick the most viable patients to address first and then maybe address people who have prolonged resuscitation.

So I think rhythm, while I agree with you is not -- first of all, you can't always say, "What is the rhythm?" because it may change momentarily and you only have one snapshot. But let's say you do have some inclination.

I would be more inclined to pick a rhythm, and it's my understanding that fibrillation or ventricular tachycardia that may be pulseless is even more of an earlier antecedent, is the appropriate consideration, because those patients in those trials, or those patients who entered those trials, have a greater, I think, propensity to have some sort of benefit.

ACTING CHAIRPERSON MAISEL: Dr. Becker.

DR. BECKER: Yes. I'd just like to make a comment that it seems to me there's another important aspect to inclusion/exclusion that we need to consider, which is sort of a new paradigm in terms of the timing of cardiac arrest and when we're providing therapies.

And a recent paper that I'd like to highlight by Dr. Weisfeldt talks about the three phases of cardiac arrest. And the notion there being that in the early phase of cardiac arrest you may have one therapy that's most appropriate, but that shortly after that there may be a totally different therapy that becomes the critical initial therapy, in the

circulatory phase or in the metabolic phase.

And so I don't think it's possible to collapse that whole audience of patients into a single study any longer with what we know in terms of the physiology of cardiac arrest. And so I think that when we think about inclusion/exclusion criteria and the communities that we're studying, you know, we have to be very careful that studies, if you will, are designed to answer the question that they seek to answer, by using the most appropriate population.

And I would just suggest that, for example, if someone were studying the metabolic phase of cardiac arrest, that it would not be appropriate to subject that therapy to all-comers in cardiac arrest, because we know that early defibrillation would be the most appropriate thing for the very early patients.

So I think that the science ultimately guides inclusion/exclusion, and I think that as the new paradigm shift occurs with the appreciation of the phases of cardiac arrest therapy, much like we would not treat a Stage I cancer protocol the same as a Stage as a Stage III cancer -- no one would do that --

you would say there would be different therapies. I think that we will have to adjust the way we look at these clinical studies as well.

ACTING CHAIRPERSON MAISEL: Dr. Halperin.

DR. HALPERIN: Yes. Cardiac arrest obviously is a -- can be a very complicated disease process -- has been pointed out. And it has a number of unique aspects that really differentiate it from other disease processes, and, in fact, the clinical trials then that are going to be designed and executed and analyzed to deal with cardiac arrest have some inherent differences.

And one of those differences is is that the -- the inclusion and exclusion criteria may not be obvious, or obtainable, at the time when patients need to be enrolled, because, in fact, data on how long the downtime is, and exactly what comorbidities may be present, which would normally be used in exclusion criteria in other studies, actually that information may not be available in a timely fashion.

And I think that, then, scientists and regulators who deal with these studies I think have to

be cognizant of those issues, and take those issues into account, so that the classic criteria that we use for designing and judging studies, maybe there should be some leeway taken to take into account the special considerations for cardiac arrest trials.

And this may include things like actually prospective criteria for inclusion or exclusion criteria that could be applied even after patients are enrolled, because, in fact, we don't want to study people who are not viable necessarily, because any intervention, as has been pointed out, would not work in patients who are completely non-viable and dead.

And, again, those are more complicated features that should be taken into account in cardiothoracic trials.

And one last comment at this point is is that, although ventricular fibrillation may be a surrogate for time in some situations, at least half, if not more, cardiac arrests that occur these days are not due to primary ventricular fibrillation. And studies of those rhythms are probably very important, so we certainly shouldn't exclude non-ventricular

fibrillation arrest trials.

And, in fact, blood flow devices actually may be more effective in those kinds of arrests than in ventricular fibrillation arrests.

ACTING CHAIRPERSON MAISEL: Dr. Normand.

DR. NORMAND: I realize we're not talking about the design right now, but it's difficult for me not to think about the design when thinking about the inclusion/exclusion criteria.

And with that in mind, and reading the material that was handed out, it seems to me that one needs to think about the latency time differently if you were to randomize. And pretend that you weren't randomizing, and I think we would think about things a little bit differently, because clearly the distributions of the populations in the various arms would be more subject to confounding.

So I think it's important obviously -- this is an obvious fact, but I think if we're talking about the inclusion/exclusion criteria, we need to think about the type of design. I realize that's further down, but I want to put that out.

It also relates to in terms of the type of data that are collected and the feasibility of including and excluding the right populations of people. So I actually would have different suggestions depending on whether or not we go a randomized trial route or if we're going down perhaps, let's say, an observational -- prospectively, well-designed observational study.

And then I'll just add one more comment, and that is related to the question about -- the latency question about time elapsed between arrest and arrival. And my simplistic understanding of the literature says either you have no idea -- if it's witnessed, you might have a single report, or you may have multiple reports.

And just, again, in terms of inclusion/exclusion criteria, I think it would be important for -- at least to get a handle on who is included and excluded is to figure out how often it's no idea, how often it's a single report, how often it's a multiple report.

And when there's no idea, that's a

different set of issues. When there are more reports, then statistically we can minimize the error, if we have multiple reports. And there are ways to refine that, but -- but, again, I think it's at least difficult for me to think operationally about inclusion and exclusion criteria without thinking about the design.

ACTING CHAIRPERSON MAISEL: Dr. Yancy.

DR. YANCY: I would concur that the design does, in large measure, dictate the population, or vice versa. But let me throw out another possibility with regard to inclusion/exclusion criteria.

I think that the data that we've been given a chance to review reflects how heterogenous the patient population is that's affected by cardiac arrest. And if we are to move this paradigm forward, we probably need to find a way to have a more uniform patient population.

There are some contradictions here in thought process, because you're talking about an immediate circumstance and emergency, so it doesn't give you the flexibility of lots of thought for going

through the process of inclusions and exclusions.

But one patient population that I do think merits a bit of thought is the hospitalized patient in a CC or critical care environment. I have the privilege of sitting in oversight of a large registry in heart failure, and I can tell you that, of over 100,000 patient episodes, there's a 1.5 percent incidence of CPR being administered. That's 1,500 patients. That's decidedly more than any of the studies we've seen.

Now, that incidence may be higher or lower for other cardiovascular illnesses, but my point is that, in an ICU setting, you can overcome the informed consent issues, because, as a matter of fact, upon admission to the ICU, these issues can be discussed. So you have that opportunity.

You may be doing a lot of prep work for low incidence, but at least you'd get around that, because in my judgment the informed consent is the most difficult part of this whole problem.

Secondly, you have the chance to learn more. I don't think that this area is as well defined